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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,554	05/02/2002	Audrey Goddard	P3230R1C001-168	9987

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 06/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,554	GODDARD ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/10/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1 – 5 are pending and under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10 April 2006 has been entered.

Priority

4. Applicant indicates that the effective filing date for the claimed invention is 24 August 2000. The examiner agrees this is the first disclosure of the claimed invention, as set forth on p. 2 of the previous office action.

Claim Rejections - 35 USC §§ 101 and 112

5. Claims 1 – 5 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

This rejection is maintained for the reasons of record and explained in further detail below. Briefly, the claimed invention is an antibody which bind specifically to the polypeptide of SEQ ID NO:48. Antibodies bind proteins, and can be useful in, for example, detection of a protein in a heterogeneous sample. Antibodies, however, do not bind to nucleic acids. The specification discloses that a small undisclosed stretch of SEQ ID NO:47 (about 200 – 600 bp, see p. 140 paragraph 0530), a nucleic acid which encodes to SEQ ID NO:48, is expressed more highly in normal stomach than stomach tumor, and more highly in rectum tumor than in normal rectum. There are no data presented as to whether the protein (SEQ ID NO:48, also called PRO994) is differentially expressed in any tumor, nor is there evidence of the utility of the antibody for diagnosis or treatment of any disease. Applicant argues extensively that the disclosure of data on nucleic acids is sufficient to confer utility on the claimed antibody, but provides no evidence as to the over- or under-expression of the protein to which the antibody

binds in any disease or condition, and also provides no evidence that the antibodies can be used for treatment or diagnosis.

Applicant argues, beginning on p. 5 of the remarks filed 10 April 2006, that the PTO has failed to adequately support the utility rejection. Applicant argues that she may substitute a reasonable correlation between evidence presented and an asserted utility in place of direct evidence on whether or not the claimed invention is useful. In this case, applicant is presenting data on the nucleic acid, PRO994 mRNA, and attempting to correlate that expression with the expression of PRO994 protein, which is to be detected by the claimed antibodies.

Applicant argues that the examiner's reliance on the article by Hu et al. is inappropriate for two reasons: 1) Hu only presents data from published literature results and is not a systematic survey of gene expression – protein expression correlations and 2) Hu et al. discuss microarray data, whereas in the instant case Example 18 is a PCR-based assay, not a microarray. The source of Hu's data are not particularly relevant to the validity and applicability to the instant case. Whether the data were pulled from existing articles or from a *de novo* experiment is not germane to the question of whether mRNA levels correlate with protein levels. Applicant also argues that the abstract by Kuo et al. teaches that there is a good correlation between mRNA and protein levels, when RT-PCR is used. Applicant provided only the abstract by Kuo; the examiner has obtained the entire article and is enclosing it herein. Kuo et al. (2005 Proteomics 5:894-906) clearly teach that the amount of mRNA and protein determined to be in a sample is highly technique-dependent. See for example p. 904, first column, where they discuss microarray data in fact correlate well with Western blot data, but not 2-D gel data, and guide the artisan to take care in determining which isoforms of a protein are present in a sample when making such correlations. In the instant case, applicant has not determined which isoforms are present in any protein samples. In fact, applicant has only presented data on nucleic acid, not protein. Thus because applicant has clearly not followed the guidance of Kuo, it is difficult to see how the article supports the position that mRNA in a nucleic acid sample is predictive of protein levels.

Applicant also argues (p. 6) that the Tokunaga reference is not sufficient to support the position that considerable further research is necessary to use the claimed invention in diagnosis of cancer. Applicant's arguments have been fully considered but they are not persuasive. Tokunaga does indeed discuss some of the difficulties in using absolute mRNA levels as diagnostics, but also points out the many problems with RT-PCR as a method. See

particularly Tokunaga, p. 380 first column, where the authors discuss how this method, the same one used by the instant applicants in Example 18, leads to false-positives, as well as detection below the level of physiological relevance. Tokunaga et al. suggest particular modifications to the RT-PCR method including use of internal controls, to prevent such problems, but applicant did not undertake any such precautions. Importantly, there is no evidence that the levels of mRNA detected by applicant are even physiologically relevant when elevated.

Beginning on p. 7, applicant argues that changes in mRNA levels are generally predictive of protein levels and offers the analogy between the nucleic acid protein situation and a car's ability to travel greater distances on greater amounts of gas. Applicant argues that because in some circumstances an increase in mRNA level leads to an increase in protein levels, the examiner should concede that the situation is more likely true than not in the instant case (see p. 9 of the remakrs). However, the reference already of record by Chen clearly shows that one cannot make this conclusion.

Applicants further contend that the limited teachings in Chen that do address changes in mRNA level support corresponding changes in the level of encoded protein. Specifically, Applicants argue that Figures 2A-2C show a correlation between mRNA/protein pairs for three specific genes, and that this supports Applicants' assertion of a correlation between mRNA and protein changes in general.

Applicant's arguments have been fully considered but are not found to be persuasive. The results in Chen shown in Figure 2A-2C represent three examples wherein protein levels were correlated with mRNA (out of 17 identified). Chen found 137 protein spots wherein protein levels were not correlated with mRNA levels. However, Chen does not report the individual variation within any of these samples (which included normal tissue and tumor tissue). Therefore, these samples may or may not have included mRNA and/or protein levels that were differentially expressed. Chen simply does not provide enough information to address the issue whether changes in mRNA levels generally result in similar changes in protein levels. All that Chen clearly teaches is that mRNA levels do not predict protein levels, as they disclose at pg 304 that "[t]he use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products, as additional post-transcriptional mechanisms, including protein translation, post-translational modification, and degradation, may influence the level of a protein present in a given cell or tissue" (see pg 304, right column).

Chen found only 17% of the genes examined had significant correlations between mRNA and protein levels (p. 311, first column). This is very clear evidence that it is not proper to conclude that there is a general correlation between mRNA and protein levels. It is particularly relevant that both Chen et al. and the instant application are dealing with samples from cancerous tissues, which quite frequently experience genetic dysregulation. Such problems can cause, for example, an overexpression at the nucleic acid level which can be compsensated for post-transcriptionally or even post-translationally. Thus when looking at cancerous tissue, it is clearly not appropriate to conclude that the changes in nucleic acid expression are representative of changes in protein expression.

Beginning on p. 10 of the remarks, applicant discusses references by Ortonft, Wang, Munaut, Hui, Khal, Maruyama, Caberlotto, Misrachi, Stein, and Guo, which applicant argues should be able to substitute for actual evidence on the claimed invention. It is important to note that none of these references, or the references cited beginning on p. 14 (i.e. Futcher, Godbout, Papotti, Van der Wilt, Grenback, Shen and Fu, or in fact any of the 113 references cited on p. 15 of the remarks) are on point to whether or not expression of the protein bound by the claimed antibody, i.e. the protein of SEQ ID NO:48, is correlated with expression of the nucleic acid that encodes it. Except for the Orntoft reference (cited at pg 31), each of the references submitted by Applicants is directed to a single gene, or a small number of genes. These references are consistent with Chen who found 17% of proteins do show correlation between mRNA and protein, and the examples of these proteins in Chen that show that changes in mRNA correlate with changes in protein level. However, these studies examining the expression of small numbers of genes are not found persuasive in view of comprehensive studies where significantly larger numbers of transcripts and proteins were examined, specifically, Nagaraja (2006), Waghray (2001) and Sagynaliev (2006) which are described below.

With regard to the Orntoft reference, Applicants submit that Orntoft examined 40 well-resolved abundant proteins, and found significant correlation between mRNA and protein alterations (including both increases and decreases) for each gene, except one.

Applicants' arguments with respect to Orntoft have been fully considered but are not found to be persuasive. Orntoft compared the mRNA and proteins levels of about 40 well-resolved and focused abundant proteins with known chromosomal locations (see pg 42). The instant specification does not teach whether or not PRO994 is a "well focused abundant" protein with a known chromosomal location as characterized by Orntoft. Furthermore, other relevant

publications (Nagaraja (2006), Waghray (2001), and Sagynaliev (2005)) report that increases in mRNA and protein samples are not correlated (see below).

The Examiner maintains the previous argument that mRNA levels are not necessarily predictive of protein levels, and in response to Applicants' arguments, maintains that this is true even when there is a changes in the mRNA level. Comprehensive studies comparing changes in expression of the transcriptome and proteome support this argument. Nagaraja (2006) teaches, "We have characterized comprehensive transcript and proteomic profiles of cell lines corresponding to normal breast (MCF10A), noninvasive breast cancer (MCF7) and invasive breast cancer (MDS-MB-231)...the proteomic profiles indicated altered abundance of few proteins as compared to transcript profiles" (See abstract of Nagaraja, 2006, Oncogene. 25: 2328-2338). Nagaraja further teaches, "The comparison of transcript profiles with proteomic profiles demonstrated that altered proteins were not always represented in the microarray designated profiles and *vice versa*" (pg 2329) and "As dictated by post-transcriptional regulation, protein profiles showed far fewer changes as compared to transcript profiles" (pg 2335).

Similarly, Waghray (2001) teaches, "we have analyzed gene expression changes induced by dihydrotestosterone (DHT) in the androgen responsive cancer line LNCaP, at both RNA and protein levels" (see Abstract of Waghray, 2001. Proteomics. 1: 1327-1338). Waghray identified transcripts from 16570 genes and found "351 genes were significantly altered by DHT treatment at the RNA level." Waghray identified 1031 protein and found 44 protein spots that changed in intensity (either increased or decreased). Twenty-nine of these proteins were identified and "remarkably, for most of the proteins identified, there was no appreciable concordant change at the RNA level (Table 4)" If changes in protein generally reflected mRNA changes, based on the fact that 2% of the genes analyzed had a change in transcript levels (351 out of 16570 genes), one would expect at least 2% of protein levels to change, or 22 out of 1031 protein spots. Therefore, it is significant that while the authors found 44 proteins that did change, very few of the identified ones had a similar change in mRNA expression.

In a review of gene expression in colorectal cancer (CRC), Sagynaliev (2006) teaches, "One thousand two-hundred and forty genes have been reported to be dysregulated (up- and/or down-regulated) in human CRC, representing about 5% of the 20000-25000 human genes" (pg 3067). Sagynaliev also teaches, "a total of 408 proteins were found to be differentially expressed in human CRC in at least one study" and importantly, "It is also difficult to reproduce transcriptomics results with proteomics tools. Out of 982 genes found to be differentially

expressed in human CRC by genome-wide transcriptomics technologies (Table 6a), only 177 (18%) have been confirmed using proteomics technologies" (pg 3068).

In summary, it is clear that Nagaraja, Waghray and Sagynaliev support that changes in mRNA expression frequently does not result in changes in protein expression. Therefore, the Examiner maintains that Applicants' measurement of an increase of PRO994 mRNA does not provide a specific and substantial utility for the encoded protein, or an antibody to the protein. Applicant has submitted several references showing that in some cases, there is a correlation between mRNA expression and the expression of the encoded protein. The PTO has provided many references that indicate that this correlation is hardly universal and that underscore the conclusion that it is improper to correlate nucleic acid and protein expression data, particularly in the case of cancerous tissue samples. Thus the state of the art of mRNA-protein expression correlations is quite clearly unpredictable. In some cases, there may be correlations, but in other cases there are not likely to be correlations. No clear generalizations can be made as to whether the expression of a protein product will change when the expression of a nucleic acid that encodes said protein changes. Applicant's assertion that it is more likely than not true that there is a such a correlation is not borne out by the evidence of record. For these reasons, the rejection under 35 USC § 101 is maintained.

6. Claims 1 – 5 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Conclusion

7. No claim is allowed

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Daniel E. Kolker, Ph.D.
June 5, 2006

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PRIMARY EXAMINER
6-5-06